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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,784	02/28/2005	Jan Balzarini	50304/061001	8526

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/525,784	BALZARINI ET AL.	
	Examiner	Art Unit	
	ABDEL A. MOHAMED	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-28 and 39-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-28 and 39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGEMENT TO AMENDMENT, REMARKS AND THE STATUS OF THE CLAIMS

1. The amendment and remarks filed 04/30/08 are acknowledged, entered and considered. In view of Applicant's request claims 23, 24 and 28 have been amended, claims 32-38 have been canceled and claims 39-42 have been added. Claims 23-28 and 39-42 are now pending in the application. The rejection under 35 U.S.C. 112, first paragraph and the partial rejection under 35 U.S.C. 112, second paragraph are maintained for the reasons of record.

2. It is noted that Applicant has amended the rejected claims under 35 U.S.C. 112, second paragraph partially as suggested by the Examiner, rendering the rejection pertaining thereto moot. Thus, the rejection for the claims which have been amended according the Examiner's suggestion have been withdrawn, but, issues in the claims which have not been amended and have been argued by Applicant are maintained for the same reasons discussed in the previous Office action as reiterated below:

CLAIMS REJECTION-35 U.S.C. 112 2nd PARAGRAPHS

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

3. Claims 25 and 26 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25 and 26 are indefinite and confusing in referring back to code numbers in the description of the application because referring back to a Table or a Figure or a Number is not acceptable claim language. Such material should be incorporated within the claim language. Further, it is long standing Office practice that claims should be completed and self-contained and incorporation into claims by express reference to the specification is not permitted and should not be relied on to define the invention (*Ex parte Fressola*, Bd. Pat. Appl. & Inter., 5/11/93, p. 1608).

Applicant has argued that claims 25 and 26 present the exceptional circumstances that justify deviation from rule that claims are to be complete. The compounds code numbers are analogous to the sequence identifiers used to identify nucleic acid and or amino acid sequences. The USPTO has recognized that it is preferable for claims to refer to these sequence identifiers, rather than reciting entire nucleic/amino acid sequences. By the same token, Applicant submits that claims 25 and 26 clearer and easier to understand as previously presented is not persuasive. Contrary to Applicant's arguments as stated in M.P.E.P. § 2173.05 "**Where possible**, claims are **to be complete in themselves**. Incorporation by reference to a specific figure or table is **permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference** than duplicating a drawing or table into the claim.

Incorporation by reference is a necessity doctrine, **not for Applicant convenience**". *EX parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993. Therefore, in view of this since the compounds referred with codes have substantially similar cores as those claimed, it would be easier for the claims **to be complete by themselves**. Further, it is not clear how the negative proviso fit in claim 25 because there is no antecedent basis in the claim. Thus, the definiteness of the claim is important to allow others who wish to enter the market place to ascertain the boundaries of protection that is provided by the claim. See *Ex parte Kristensen*, 10 USPQ 2d. 1701, 1703 (PTO Bd. App, & Inter. 1989). Hence, in order to obviate the above rejection, it is suggested again that Applicant amend the claim to particularly point out and distinctly claim the subject matter, which Applicant regards as the invention.

CLAIMS REJECTION-35 U.S.C. 112 1st PARAGRAPHS

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28 and newly presented claim 39 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments filed 04/30/08 have been fully considered but they are unpersuasive. Applicant has argued that the rejection of claim 28 was based on the recitation of one or more compounds according to claim 23 and one or more compounds effective in the treatment or prophylaxis of viral infections "in proportions such as to provide a synergistic effect in the said treatment or prophylaxis." The reference to proportion providing a synergistic effect has been deleted from the claim. As amended, claim 28 teaches to a composition containing at least one of the compounds of the invention in combination with at least one compound that is effective in the treatment or prophylaxis of viral infection. Although certain combinations are expected to have additive or synergistic effects with respect to prophylaxis and treatment of viral infection, this is not a requirement of amended claim 28. The specification enable one skilled in the art to produce compounds according to claim 23. To practice claim28, one must simply add another anti-viral compound to one of the claimed compounds. As this is clearly within the level of skill in the art in view of the guidance provided in the specification, withdrawal of the rejection is thereof requested is unpersuasive.

Contrary to Applicant's arguments as stated in the previous Office action, the instantly claimed invention as claimed in amended claim 28 and newly submitted claim 39 is directed to a composition comprising one or more compounds according to claim 23 and one or more compounds effective in treatment or prophylaxis of viral infections selected form the group consisting of Retroviral, Flaviviral, Herpes and Coronaviral enzyme or entry inhibitors. However, the specification does not enable compositions for

use in the prevention or treatment or prophylaxis of viral infections in general as claimed in claims 28 and 39, and in particular the various families of viral infections and the numerous glycopeptide antibiotics and derivatives thereof in the manner claimed in independent claim 23 because there are no working examples or data cited in the instant specification, except for the general methods and materials for the preparations of the compounds, representing the structures of the prepared compounds, and determination or evaluation of antiviral and cytostatic/cytotoxic activity of the compounds as exemplified by the Examples and Tables in the instant specification. Example 1 and Tables 1 to 8 represent the structures of the prepared compounds as examples and their respective codes. Example 2 shows general methods and materials for the preparation of the compounds. Examples 3 and 8-13 disclose methodologies for determination of antiviral and cytostatic/cytotoxic activities. Examples 4 and 5 demonstrate evaluations of cytostatic and anti-HIV activities of the compounds. Examples 6 and 7 teach anti-HIV-1 and –HIV-2 activities of some compounds in different cell lines.

Further, the reference of Balzarini et al (all three inventors are authors of this reference) in Antiviral Research, 2006, Vol. 72, pages 20-33 states in the abstract that various semisynthetic derivatives of glycopeptide antibiotics including vancomycin, eremomycin, teicoplanin, ristocetin A and DA-40926 have been evaluated for their inhibitory activity against feline infectious peritonitis virus (FIPV) and human (SARS-CoV, Frankfurt-1 strain) coronavirus in cell culture in comparison with their activity against human immunodeficiency virus (HIV). On page 21, left column, second

paragraph the reference continues by stating that while we could demonstrate that several lipophylic derivatives of the glycopeptide antibiotics, including a variety of aglycon derivatives, showed anti-coronavirus activity in the lower micromolecular range, there was not a close structure-activity relationship for the glycopeptide derivatives against both viruses, suggesting that at least for this particular class compounds, the FIPV cell culture model cannot be regarded as reliable surrogate model to screen for efficient anti-SARS-CoV inhibitors. The fact that the molecular target (peptidoglycan synthesis) for antibacterial activity is entirely absent in viruses and mammalian cells, and the glycopeptide antibiotics are use worldwide for the treatment of infections caused by bacteria, particularly by Gram-positive bacteria.

The reference concludes by stating that some of the compounds inhibited virus infection in the lower micromolar range without measurable cytotoxicity at 80-100 μM. Although the molecular mechanism of anti-HIV and anti-FIPV action is likely to be the viral entry process, no close correlation could be established between the activity of the compounds against HIV-1 and both coronaviruses, or between their activities against SARS-CoV and FIPV. It would appear, therefore, that the FIPV model is not an adequate surrogate model for detecting specific anti-SARS coronavirus inhibitors within the structural class of glycopeptide antibiotics. Further, the instant specification acknowledges by stating on page lines 19 and 20 that the viral infection remain a major medical problem worldwide because of a lack of therapy, prevention or vaccination strategy and because of the rapid development of resistance.

Furthermore, the reference of Nagarajan et al (U.S. Patent No. 4,698,327) in col. 1, lines 43-55 states that in the search for new antibiotics, structural modification of known antibiotics is attempted whenever possible Many antibiotics, including the glycopeptides, however, have such complex structures that even small changes are difficult to make. Furthermore, it is difficult to predict the effect these changes will make in the desired activity. Processes for modifying known antibiotics and the new derivatives made by such processes continue, therefore, to be of great importance. Moreover, as acknowledged on page 5, lines 22-29 in the instant specification, Applicant states that emerging bacterial resistance to vancomycin, which has recently become a major public health threat, is a stimulus for synthesis and investigation of various derivatives of glycopeptides antibiotics, and cites several references which describe novel glycopeptide antibiotics related to vancomycin with antibacterial activity. However, none of these compounds or their derivatives has been demonstrated to have antiviral properties or to be suitable to inhibit or prevent viral infections. Among the references cited Malabarba et al (Med. Res. Rev. Vol. 17, No.1, pages 69-137, 1997) provided previously by Applicant on IDS filed 12/26/06 teaches various modifications of the vancomycin core to modify the properties and concludes, "The structural complexity and abundance of functionality characteristics of the glycopeptides antibiotics presents a seemingly formidable challenge to the medicinal chemist. The result presented show that selective chemical derivatization offers the possibility of enhancing the antibacterial activity of glycopeptides....There is still much to be learned about the chemical reactivity and therapeutic potential of this important class of antibiotics." (Page 135).

Therefore, in view of the above, there is no data or activity in the instant specification showing the use of the various claimed compounds for preventing or treating all kinds of viral infections by administering the compounds of claim 23 in the manner claimed in claims 28 and 39 in the instant invention. Applicant has not provided even **one example** as claimed, except for the general method and materials for the preparation of the compounds and various *in vitro* assays for the methodologies for determination of antiviral and cytostatic/cytoxic activity in various cell cultures. From this Applicant is attempting to extrapolate to a broad diversity of glycopeptide antibiotics or derivatives thereof for preventing and/or treating all kinds of viral infections in which the effects of the claimed glycopeptide antibiotics and derivatives thereof are unknown for the reasons discussed above, and as such, when this variable is added, the claimed invention becomes little more than conjecture. Moreover, without guidance, the use of various glycopeptide antibiotics and derivatives thereof in general for the prevention/prophylaxis and/or treatment of viral infections in the manner claimed is unpredictable in view of the references of Balzarini et al, Nagarajan et al and Walabarba et al as discussed above, and as such, the experimentation left to those skilled in the art is unnecessary and improperly, extensive and undue. See *Amgen Inc. V. Chuqai Pharmaceuticals Co. Ltd.*, 927 F.2d, 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Therefore, the scope of the instantly claimed invention is speculative in claiming a composition comprising one or more compounds according to claim 23 and one or more compounds effective in treatment or prophylaxis of viral infections selected from

the group consisting of Retroviral, Flaviviral, Herpes and Coronaviral enzyme or entry inhibitors as claimed in claims 28 and 39 for the reasons discussed above.

Therefore, without guidance through working example(s), one of ordinary skill in the art would not predict from *in vitro* assays data disclosed in the instant specification to administer the claimed compounds for prevention and/or treating all kinds of viral infections in patients including humans in the manner claimed in the instant invention in view of the references of Balzarini et al (3 of authors of the reference are inventors of the instant invention), Nagarajan et al and Walabarba et al and in view for the reasons discussed above. Secondly, the Examiner has clearly shown in the previous Office action of Paper No. 20071022 (mailed 10/31/07) that the specification does not enable any person skilled in the art to which it pertains, or which is most nearly connected, to use the invention commensurate in scope with the claims. In the express absence of one or more examples, evidence and sufficient guidance, the skilled artisan would be faced with undue experimentation for practicing the invention. Thirdly, it is not understood from Applicant's response how the instant invention, which Applicant considers as novel and inventive composition effective in the treatment or prophylaxis of viral infections be exemplified without working example(s) or data or evidence. The law requires that a disclosure in an application shall inform those skilled in the art how to use Applicant's alleged discovery, not how to find out how to use it for themselves. See *In re Gardner et al.*, 166 USPQ 138 (CCPA 1970). Thus, the specification does not enable any person skilled in the art to which it pertains, or which is most nearly connected, to use the invention commensurate in scope with the claims. In the express

absence of one or more examples, evidence and sufficient guidance, the skilled artisan would be faced with undue experimentation for practicing the invention.

CLAIMS REJECTION-35 U.S.C. § 102(b), 102(e)

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 23 is rejected under 35 U.S.C. 102(b) as being anticipated by Cooper et al (U.S. Patent No. 5,977,062).

The instantly claimed invention of Formula I and II as drafted in claim 23 is directed to glycopeptides antibiotic. The prior art of Cooper et al ('062 patent) discloses a glycopeptides antibiotic formula which is substantially the same as the claimed Formula I and II of claim 23. Therefore, the formula of '062 patent clearly encompasses Formula I and II as claimed in claim 23, in the absence of evidence to the contrary, the reference's glycopeptides antibiotic formula anticipates the claimed glycopeptides antibiotic Formula I and II as drafted in claim 23.

OBJECTION OF THE CLAIMS

6. Claim 23 is objected on page 4, lines 6, after "bond" in ending in period. Also, in line 5 "b5" should be --b^5--.

On page 4, claim 23 is confusing in the recitation "R^d represent R", "R^c represent R" and "R^{5c} represent R^5", and in claim 24, page 7, line 9, in the recitation "Y represents oxygen" and in line 14, "Y represents hydrogen", etc. The claims are so much disjoined and they are not clear because there are so many variations. Appropriate correction is required.

Claim 24, page 9, lines 1 and 2 is not understood by the recitation "glucosyl-2-O-Leu and their derivatives. Also, on page 9, lines 3 and 5, use of Markush format is suggested so that the claim will be consistent with other Markush formats.

CONCLUSION AND FUTURE CORRESPONDANCE

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABDEL A. MOHAMED whose telephone number is (571)272-0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mohamed/A. A. M./
Examiner, Art Unit 1654

/JON P WEBER/

Supervisory Patent Examiner, Art Unit 1657